The unique challenges of clinical trials in rare disease: A regulatory writer's perspective

Sarah Milner, **Andrew R. Kusmierczyk**, **Julie Taccoen**
PTC Therapeutics, Inc. South Plainfield, NJ, USA

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Correspondence to:
Sarah Milner
smilner@ptcbio.com

Abstract

Designing clinical trials in rare diseases comes with a specific set of challenges including limited knowledge around the natural history of a disease, small sample size available for trial participation, regulatory guidance that is not calibrated to the rare disease context, manufacturing and supply issues, and safety and financial risks. Here, we discuss some of these potential challenges and how, through proactive early engagement with key opinion leaders, regulatory bodies, and patient groups, a cohesive and strategic clinical development plan can be created to provide the strongest foundations when marketing approval is sought.

Introduction

Clinical trial design is inevitably complex in any context, but in a rare disease with a paediatric population, the task can seem insurmountable. The EMA defines a disease as "rare" if it affects less than 5 in 10,000 of the EU general population.[1] Although individual rare diseases may affect fewer than 100 patients, collectively it is estimated that over 30 million people in the EU live with a rare disease, of whom 30% are children who will die before the age of 5.[1,2] It is estimated that only 6% of all known rare diseases have available treatments, highlighting the need for new therapies.[2]

It is widely acknowledged that industry, academia, regulators, healthcare providers, and others need to collaborate to meet this need for new therapies, but the drug development and trial process is complex with ethical, scientific, operational, and regulatory considerations. Here, we describe some of the key challenges and propose proactive solutions with the aim of getting new, safe, and efficacious treatments to patients with significant unmet medical needs.

Regulatory interaction and incentives

Development of drugs for the treatment of rare diseases carries more financial risks compared with mainstream drug development; A smaller population entails a higher rate of study failure (as every patient has numerically and statistically more impact on results) and less opportunity for returns and recovery of drug development costs. Recognising this, the EMA and European Commission offer "orphan designation" to incentivise companies to develop rare disease treatments.[3]

Currently, if awarded orphan designation, companies benefit from free protocol assistance and 10 years of market exclusivity on approval. A further incentive of an additional 2 years of market exclusivity is awarded to companies who include results of paediatric studies for a medicine with orphan designation. As a sidenote, it is anticipated that orphan drug designation classification requirements and rewards are under review with draft guidance anticipated in 2023.

To qualify for orphan designation, the company must demonstrate that the condition is "rare", that the condition is life-threatening or chronically debilitating, and that the medicine is of significant benefit to those affected by the condition. Establishing these can be challenging, and companies often must get creative using deep data mining techniques and extensive literature searches to find the data required.

Designing a clinical trial

A number of crucial issues must be considered in designing a successful clinical trial, especially in a rare disease population.

What is the objective?

When deciding on the objective of a trial, it is important to consider the bigger picture of the drug development plan (and how the trial fits within the overall drug development plan) and to design a trial with an eye on the ultimate goal, which may be a marketing authorisation application. The next step is defining what the trial is intended to address: "What are you hoping to show?" and "Why does it matter?" This could be a demonstration of superiority in comparison with standard of care, non-inferiority in comparison with standard of care, or simply gaining a greater understanding of the natural history of the disease.

Undoubtably, planning the study design and objective(s) requires an understanding of the natural history of the disease, the disease pathology, and the competitive landscape. Unfortunately, for many rare diseases, little research exists and the diseases are frequently not well-characterised, which means that finding relevant literature and source materials can be challenging. Additionally, competitors are often non-existent. Consequently, engaging in close collaboration with patients, patient advocacy groups, specialist healthcare professionals, and subject matter experts is important to ensure that the objective(s) for the trial is clinically meaningful to patients in a "real-life" context.

Once these objectives are defined scientifically, it is important that the company reaches out to the EMA to validate and confirm the adequacy and acceptability of the proposed objectives from a regulatory standpoint for the study.

Patient population

The patient population selected for the pivotal clinical trials should be representative of the therapeutic indication for the product's planned marketing authorisation and product label, so it

is vital to get this correct from the outset for the potential success of the trial. Selecting the wrong population can also impact recruitment, which in turn can negatively affect the duration of the study.

A fine balance is needed when considering the patient population for a clinical trial: The inclusion and exclusion criteria need to be wide enough to enrol the maximum number of patients without being so general that too much variability (or "noise") is introduced that can dilute the results.

Putzeist reports that failure to identify the most appropriate target population was a key feature of failed orphan marketing authorisations, emphasising the criticality of identifying the appropriate patient population from the start of clinical development.[4] The patient pool is limited in rare disease; Therefore, careful definition of the population is key.

Setting inclusion and exclusion criteria can be tricky with rare diseases as they are typically not well characterised due to lack of available natural history data and a limited in-depth knowledge of the underlying disease pathology. Additionally, given that these diseases often disproportionally affect children, the situation becomes more complex. It is also to be considered that different countries follow different national guidance on diagnosis and treatment, and if the planned trial involves a non-standard parameter in the inclusion and exclusion criteria, it can affect recruitment of both investigators and patients who feel that participation is burdensome.

Choice of study design

The message from EMA is clear on expectations around study design: "Most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials (RCTs) that follow generally accepted rules and guidance." However, the EMA does acknowledge that "a comparative trial will usually be preferable but may not always be possible".[5]

An RCT is well-recognised as the gold standard for an unbiased evaluation of effects to support marketing approval. In an RCT, patients are randomised (usually 1:1) to two (or more) groups to test a new drug compared with placebo or standard or care. An endpoint (defined as "an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial") is measured at specific time points and the results are compared between groups; any differences are tested statistically. This is the ideal design that any pivotal trial should use to gain an unbiased estimate of benefit and risk.

Unfortunately, a clear limitation of RCTs in a rare disease is a smaller number of available potential patients. To support a successful EMA Marketing Authorisation, rare disease pivotal studies may enrol as many as several hundred of patients or as few as less than 30 patients, dependent on the specific disease. This is in contrast to typical RCTs for diseases that are not considered rare, which must enrol more patients for adequate statistical powering and demonstration of significant differences between treatments.

An additional concern with rare diseases is that, even within one specific condition, there is often considerable clinical, mutational, and phenotypical variability between patients, which can complicate interpretation of results.

Innovative adaptive study designs, use of historical controls, and alternative statistical approaches may be acceptable if they help improve the interpretability of the study results. One recommended approach is the use of a cross-over design where patients receive one treatment, followed by a washout phase, and then receive the other treatment. However, this results in a longer trial with two treatment periods, which can raise significant ethical concerns in progressive irreversible diseases and can impact patient recruitment and retention.

Types of controls

The ICH E10 guidance provides direction on the choice of control groups in clinical trials and outlines different options: 1. placebo, 2. no treatment, 3. different dose/regimen of study drug, 4. different active treatment, or 5. external (historical).[6] Options 1 through 4 are concurrent controls (control and test groups are chosen from the same population and treated concurrently).

Option 1 The use of a placebo is generally optimal, as it allows the clearest demonstration of benefit and risk of a treatment. However, this can be problematic as patients with rare diseases are often children who are gravely ill and do not want to take the gamble that they may be randomised to a treatment that has zero therapeutic benefit. In this situation, either a cross-over design (placebo followed by active or vice versa) or an open-label period after a placebo period can prove highly effective as patients are 100% guaranteed to receive active drug.

Option 2 (no treatment) presents an alternative approach. In a no-treatment-controlled trial, patients are randomised to either study drug or no treatment; however, bias can be introduced as it is not possible to blind the investigator and patients and subjectivity becomes a concern.

A useful approach in this type of study is to include a blinded panel of assessors to permit an objective independent evaluation of outcome measures, but it does not solve the inherent possible bias of any patient-assessed outcome. This option can also provide useful data on the natural history and progression of a disease, which is often a relative unknown in many rare diseases.

Option 3 (different dose/regimen of study drug) presents with similar practical and ethics issues as Option 1 where either a placebo or an active-control group is included.

Option 4 (different active treatment) can, generally, be disregarded with rare diseases given that only 6% of rare diseases have treatment options available.[2]

Option 5 (external control [including historical control]) is an interesting alternative that has recently gained a lot of attention within the rare disease world. Specifically, a "virtual" control is formed from patients with the same disease from sources such as ongoing patient registry studies, medical records, and control populations from previous trials. This allows a company to compare their treatment effects essentially against standard of care and/or natural disease progression. However, this approach needs to be used with great caution at the design, analysis, and interpretation stages. To avoid bias, the definition of which patients to include must be tightly controlled to ensure that only patients with very similar disease states, demographics, and medical history are used in the control group.

It is also important to consider that if the study involves a specific efficacy outcome measure, patients in the control group may also need to have data available from that assessment. This can be challenging if the outcome measure is not commonly used, which is a common problem with rare diseases where diagnostic and treatment approaches vary enormously. Despite the potential obstacles of using real-world evidence, the EMA has shown willingness to accept studies with historical controls, but it is crucial to validate this approach with the EMA upfront before conducting the study as it has clear limitations and can impact in terms of future marketing authorisation.[5]

Selection of endpoints

In general, in any kind of trial, including those conducted in rare disease, monitoring of safety through incidence and frequency of adverse events (alongside other safety parameters) form a key endpoint for assessment of benefit/risk of study drug. An efficacy endpoint can be defined as "an event or outcome that can be measured objectively to determine whether the intervention being studied is effective".[7] Alongside the primary endpoint (essentially the measurement tool that is predefined as the main way of answering the question the trial poses), secondary and exploratory endpoints can be crucial to demonstrate the overall benefit in diseases that are less well categorised and should be carefully selected.

In rare diseases, disease-specific clinical endpoints often do not exist due to the limited patient population and lack of natural history data. If disease-specific clinical endpoints do exist, they are frequently unvalidated, not well recognised, or not commonly used in the clinic. Reaching out to patient groups to help understand what endpoints are meaningful for patients is important and, crucially, will support the overall patient benefit claim when seeking marketing authorisation.

In addition to direct clinical outcomes, if available, companies should consider patient-reported outcomes, surrogate (indirect measurement of effect) endpoints, and biomarker analyses that can be linked to clinical benefit to satisfy both EMA requirements and the unmet medical need in patients. It is noteworthy that both surrogate endpoints and biomarker analyses have been used, albeit at times with controversy, to successfully gain conditional (provisional) marketing authorisation for orphan drugs in the EMA.

To this end, it is crucial to get agreement from EMA on endpoint selection and validation as early as possible in the clinical development programme. Fortunately, EMA has recognised this obstacle and companies can request an opinion on the acceptability of a novel biomarker as an endpoint or the use of a surrogate endpoint. Early engagement ensures documented agreement between the EMA and the company that the selected endpoints will provide suitable efficacy data to support marketing approval at a later stage.

Other considerations

Engaging the patient community

Dialogue with patients and patient advocacy and alliance groups is crucial as it allows real-world information to be collected and identifies what improvements would be seen to be significant in the eyes of those experiencing the disease first hand. Importantly, this dialogue begins to establish the process of building trust with the rare disease patient advocacy community. Individuals living with rare diseases may be wary of a healthcare system that is often ill-equipped to diagnose and treat them; Some may have gone through numerous providers, procedures, misdiagnoses, and treatments before even receiving the correct diagnosis. Therefore, to maximise patient compliance and adherence to a clinical trial regimen (and eventually to the approved treatment), companies are well-advised to invest in establishing a relationship with the patient community that is founded on trust.

Geographic dispersion of patients, sites, and investigators

In rare disease, to find the patients, first you must find the treating physicians and convince them to be investigators on your trial. Finding investigators with specialisation in a rare disease can be challenging, and resources such as the Orphanet database, the European Organisation for Rare Disease, and the National Organization for Rare Disorders can aid greatly with this process.[8–10] Investigators can also be found by looking at who participated in previous trials, disease key opinion leaders, and internet/literature searches. It is important to consider when identifying sites and investigators that compliance with global healthcare standards and Good Clinical Practice (GCP) vary around the world. Trials must be GCP-compliant, and outreach and audits to assess this are critical to ensure safety of patients and veracity of data collected. It is inevitable that the more sites, the more challenges arise, and

engagement of local expert contract research organisations aids cultural, linguistic, and procedural differences.

Study drug manufacture and formulation

Planning drug manufacture, supply, and management in rare disease trials presents unique logistical challenges, and selection of an experienced logistics contract research organisation or partner is key.

Orphan drugs are often extremely expensive to manufacture as specialist facilities and equipment are required; Thus, they are initially produced in very small quantities, sometimes even at the individual patient-level. Once safety and efficacy are initially shown and Phase 3 trials are planned, the scale up process begins to ensure enough drug is available. This may involve generation of a commercial "Phase 3" formulation that can be produced faster and more efficiently than the initial formulation. However, this comes with associated requirements such as relative bioavailability studies to show the new formulation is comparable to the preliminary formulation. Notably, as the clinical development programme progresses, it may be necessary to develop and test formulations for specific populations (eg. paediatrics and patients with difficulties swallowing).

Conclusions

Orphan drug development is a hugely expanding area but is undoubtably challenging with no conventional roadmap to follow. Through proactive early engagement with key opinion leaders, regulatory bodies, and patient groups, a cohesive and strategic clinical development plan can be created to provide the strongest foundations when marketing approval is sought.

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Author information

Sarah Milner, PhD, joined PTC Therapeutics, Inc. in 2020. She is an associate director of scientific writing and is passionate about encouraging women in STEM.

Andrew R. Kusmierczyk, PhD, joined PTC Therapeutics, Inc. in 2022. He is an associate director of CMC technical writing and is intrigued by all manner of scientific communication.

Julie Taccoen joined PTC Therapeutics, Inc. in 2017 and is a senior director of regulatory affairs (Europe).